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EXAMINER

BARTON, JEFFREY THOMAS

ART UNIT PAPER NUMBER

1753

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/057,354

Applicant(s)

BOHM ET AL.

Examiner

Jeffrey T. Barton

Art Unit

1753

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 5-24, 26-48 and 50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-24, 26-48, and 50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. The amendment filed on 14 April 2006 does not place the application in condition for allowance.

Status of Rejections Pending Since the Office Action of 14 October 2005

2. All rejections of claim 49 are obviated due to the cancellation of the claim.
3. The rejection of claims 1-3, 5-24, and 26-49 under 35 U.S.C. §112(2) is withdrawn due to Applicant's amendment.
4. All other previous rejections are maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 50 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no disclosure of the meniscus described in this claim in the application as originally filed. The figures uniformly show menisci

with outer edges aligned with the bottom of the injection port, with the lowest point of the meniscus aligned with no portion of the sidewall. The specification text provides only the most general description of meniscus shape (Page 10, lines 6-20), with no explicit description of "an inner edge of the meniscus align[ed] with an inner surface of the side wall and an outer edge of the meniscus align[ed] with an outer edge of the side wall".

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 2, 5-8, 30-37, 39-41, 43, 44, 46-48, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al (WO 99/64850) in view of either McCormick et al or Amigo. Since WO 99/64850 is in German, citations below are given to US Patent No. 6,846,398, which issued from the National Stage entry of this International Application.

Relevant to claims 1 and 46-48, Heller et al disclose a separation device (Figures 1 and 2) comprising: anode and cathode reservoirs (P1 and P2); a plurality of channels connected to the anode reservoirs with each of the channels having an interior bounded by a side wall; a plurality of interface ports (A) formed in the sidewalls of the channels to provide access to the channel, each of the ports having a depth equal to the sidewall (i.e. cover) thickness (Column 6, lines 1-2); with the anode and cathode reservoirs multiplexed with the channels. (Figure 1)

Relevant to claims 30 and 32, Heller et al disclose a separation device comprising: a substrate (Chip C; Column 4, lines 35-37); a plurality of channels formed in the substrate (Figures 1 and 2), each channel having an interior bound by a side wall; a plurality of interface ports (A) that provide access to the interiors of the channels

(Figure 2; Column 6, lines 1-2); an anode reservoir multiplexed to two or more separation channels; and a cathode reservoir multiplexed to two or more separation channels (Reservoirs P1 and P2; Figure 1)

Relevant to claim 39, Heller et al disclose a method of injecting a liquid into their separation device, comprising: connecting a cathode reservoir to the respective first ends of two or more channels; connecting an anode reservoir to the respective second ends of these channels (Figure 1; Column 4, lines 27-31; construction of the device inherently includes steps as recited); forming a droplet of the sample and directing it through an interface port (Column 6, lines 20-28 and 50-52); and applying a voltage to the port in order to inject the sample into the channel. (Column 3, lines 30-32; the charged pin will inherently carry a voltage to the port in the injection step)

Relevant to claims 40 and 43, Heller et al disclose a method of forming a separation device comprising the steps of: forming a plurality of separation channels in the device, each channel being defined by an interior bounded by a side wall; forming a plurality of fluid interface ports (Figure 2, port A) leading to the channels; connecting an anode reservoir to two or more channels; and connecting a cathode reservoir to two or more channels. (Column 4, lines 27-31; construction of the device inherently includes steps as recited)

Relevant to claims 2 and 34, Heller et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Figure 1; Electrodes E1-E4)

Relevant to claim 6, Heller et al disclose such an array of apertures (Figures 1 and 2)

Relevant to claims 7, 31, 33, 41, and 44, Heller et al disclose channel widths of 20 - several hundred microns, and the port diameter is bounded by the channel width. (Figure 2; Column 4, lines 61-62; Column 5, lines 21-25)

Relevant to claim 8, Heller et al disclose their device being a capillary array electrophoresis plate. (Figure 1; Column 1, lines 5-10)

Relevant to claim 35, Heller et al disclose the regular spacing of the interface ports such that they can receive solutions from a parallel loading device. (Column 6, lines 20-28)

Relevant to claims 36 and 37, Heller et al disclose a parallel loading device comprising a multi-headed pipetter or pins for carrying droplets. (Column 6, lines 20-22)

Regarding the independent claims, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as "coplanar" with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Heller et al do not explicitly disclose the thickness of their cover, which is pertinent to the dimensional limitations of the instant claims, an interface port wider than it is deep, or a "virtual wall" meniscus.

McCormick et al disclose a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns.

(Column 13, lines 17-22)

Amigo discloses a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 8, lines 1-6)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device and methods of Heller et al by specifically using a cover as thin as 10 microns, as taught by either McCormick et al or Amigo, because the silence of Heller et al concerning this indicates that a skilled artisan could choose any suitable cover thickness such as those known in the prior art, e.g. McCormick et al or Amigo. The choice of thinner material could be motivated by reduction of material consumption, which could potentially reduce manufacturing costs.

Designation of a channel as a “separation” channel in structural limitations is not given undue weight in these rejections, as it points to an intended use of a device rather than defining a specific structure. Each section of “injection” channel associated with a particular “separation” channel in Heller et al is referred to as a separate channel, although all are joined. (Column 7, lines 6-12) However, some separation of charged components of different charge to mass ratios will inherently occur upon exposure to a DC electric field, such as during the injection as described by Heller et al. Additionally,

Heller et al disclose that sample migration in the "injection" channel beyond the intersection with the "separation" channel need not occur. (Column 5, lines 59-63) In effect, this results in the "separation" channel running from the injection port to the downstream reservoir, as the separation will commence upon the first exposure of the injected sample to an electric field. (i.e. between electrodes E3 and E4)

Regarding the independent claims, within this combination, with a channel and port width of twenty to hundreds of microns (Column 4, lines 61-62; Figure 2) and cover thickness of 10 microns, the limitation to a port diameter significantly larger than its depth is met.

Regarding the limitations to a "virtual wall" and port dead volume of less than a picoliter or zero, Heller et al provide no explicit disclosure except that all channels in their system are filled with a separation medium (Column 5, lines 66-67), and therefore a medium/air interface will exist at these ports. Whether the medium forms a meniscus at the interior or exterior surface of the port depends on the cross-sectional area of the port vs. that of the channel - fluid will naturally be drawn into the narrower opening, driven by its surface tension. While no explicit channel depth is recited by Heller, a shallow channel could obviously be used (e.g. about twice as wide as it is deep, as conventionally results from isotropic glass etching). An approximately hemicylindrical 100 micron wide, 50 micron deep channel would have a cross section of 1250π square microns, while the port configuration of Figure 2 of Heller et al for this channel would be a circle with 100 micron diameter, having a cross section twice as large. In the absence of applied pressure, fluid in the channel would not be drawn into the port to a significant

extent, and the meniscus would form at the bottom surface of the wall, leading to a port dead volume of substantially zero. Given a conventional flowable separation medium, this meniscus could only correspond to the instantly claimed "virtual wall", as no distinction between the respective ports, associated channels, or fluids can be seen. In addition, relatively deep channels with larger cross section than that of the port taught by Heller et al could also obviously be used, and in such cases fluid would be drawn into the port, forming a meniscus according to the limitations of claim 50.

11. Claims 1-3, 5-8, 12-24, 26, 30-36, and 38-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al in view of Howitz et al.

Relevant to claim 1, Simpson et al disclose a separation device (Column 1, line 65 - Column 2, line 1) comprising: one or more anode reservoirs (Figure 1, 180; Column 9, lines 25-27)); a plurality of separation channels connected to the anode reservoirs (Column 3, lines 14-28; Column 9, lines 25-27), with each of the separation channels having an interior bounded by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); a plurality of fluid inlets to the separation channels (Figure 2, B and C with associated channels to channel 222); and at least one cathode reservoir multiplexed with two or more separation channels. (Figure 1, Reservoir 120)

Relevant to claim 12, Simpson et al disclose a separation device comprising: an array of microfabricated separation channels formed at the surface of a first microfabricated substrate and a corresponding surface of a second substrate bonded to the surface of the first substrate with each channel having an interior bounded by a

sidewall, a first end and a second end (Figures 1 and 4B; Column 9, lines 12-17; Column 4, line 47 - Column 5, line 7); an array of fluid inlets to the separation channels (Figures 1 and 2, B and C with associated channels to channel 222); an array of cathode reservoirs connected to the first end of each of the separation channels (Figure 1; Column 9, lines 23-24); and an array of anode reservoirs, wherein at least one anode reservoir is connected to the respective second ends of at least two of the separation channels. (Figure 1; Column 9, lines 25-27)

Relevant to claims 30 and 32, Simpson et al disclose a separation device comprising: a substrate (Column 4, line 47 - Column 5, line 7); a plurality of separation channels formed in the substrate (Column 3, lines 14-28), each channel having an interior bound by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); a plurality of fluid inlets to the separation channels (Figure 2, B and C with associated channels to channel 222); an anode reservoir multiplexed to two or more separation channels (Figure 1, Reservoir 180; Column 10, lines 49-57); and a cathode reservoir multiplexed to two or more separation channels (Figure 1, Reservoir 120; Column 10, lines 58-65)

Relevant to claims 2, 16, 17, 22, and 34, Simpson et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Column 5, line 36 - Column 6, line 37; Column 10, lines 9-10) This array can be in electrical contact with the device (Figure 4B; Column 10, lines 31-33), or integral with the substrates of the device (Column 10, lines 11-13).

Relevant to claim 3, Simpson et al disclose a separation device with an outer perimeter and a center, with the separation channels connecting the outer perimeter to the center. (Figure 9; Column 9, lines 9-11)

Relevant to claims 8 and 26, Simpson et al disclose their device being a capillary array electrophoresis plate. (Column 1, lines 65-66)

Relevant to claim 14, Simpson et al disclose the first and second substrates being made of glass. (Column 9, lines 66-67)

Relevant to claim 15, Simpson et al disclose the first and second substrates being made of plastic. (Column 10, lines 1-2)

Relevant to claims 18 and 35, Simpson et al disclose the regular spacing of the fluid inlets on one of the substrates to receive solutions from a parallel loading device. (Column 1, lines 13-15; Column 4, line 47 - Column 5, line 7)

Relevant to claims 19 and 24, Simpson et al disclose the first substrate of their device including an array of electrodes aligned with sample reservoirs of the device to make electrical contact with solutions in the sample, waste, anode, and cathode reservoirs. (Column 10, lines 17-23)

Relevant to claim 20, Simpson et al disclose a number of holes, H , approximately equal to $5N/4$, where N is the number of samples to be processed. (Column 10, lines 24-27)

Relevant to claim 21, Simpson et al disclose their device being made of a combination of glass and plastic. (Column 10, lines 28-30)

Relevant to claim 23, Simpson et al disclose a plurality of sample fluid inlets in communication with one of the separation channels (e.g. Figure 2, B and C both feed channel 222)

Relevant to claim 36, Simpson et al disclose a parallel loading device comprising a multi-headed pipetter. (Column 11, lines 16-18)

Relevant to claim 38, Simpson et al disclose the disposition of the separation channels in a radial pattern on the separation device. (Figure 9)

Relevant to claim 39, Simpson et al disclose a method of injecting a liquid into their separation device, comprising: connecting a cathode reservoir to the respective first ends of two or more channels (Column 11, lines 29-30); connecting an anode reservoir to the respective second ends of these channels (Column 11, lines 31-32); loading a sample liquid into the sample reservoir; and applying a voltage to inject the sample into the separation channel. (Column 8, lines 32-41; Column 11, lines 33-41)

Relevant to claims 40 and 43, Simpson et al disclose a method of forming a separation device comprising the steps of: forming a plurality of separation channels in the device (Column 11, line 49), each channel being defined by an interior bounded by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); forming a plurality of sample reservoirs connected to the channels (Column 11, lines 50-54); connecting an anode reservoir to two or more channels (Column 11, lines 55-56); and connecting a cathode reservoir to two or more channels. (Column 11, lines 66-67)

Relevant to claims 42 and 45, Simpson et al disclose the radial disposition of the channels on the separation device. (Figure 9)

Regarding the independent claims, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as “coplanar” with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Simpson et al do not explicitly disclose a device comprising: fluid interface ports formed in the side walls of the separation channels to provide access to the interiors of the separation channels, wherein the diameter of the port is significantly larger than its depth, wherein a separation medium disposed in the interior of the separation channel forms a virtual wall at each fluid interface port, and wherein each fluid interface port has a dead volume less than about 1 pL (Claim 1), zero dead volume (Claim 5), or diameters between 25 and 125 μm . (Claims 7, 13, 25, 31, 33) They also do not explicitly disclose a fluid interface port that comprises an array of apertures forming virtual walls. (Claim 6)

Regarding claim 39, Simpson et al do not explicitly disclose forming a droplet from the liquid sample, or directing the droplet to a virtual wall formed by a separation medium in a fluid interface port formed in the sidewall of a separation channel.

Regarding claims 40-45, they also do not explicitly disclose a method comprising forming the plurality of ports in the channel sidewalls by removing portions of the sidewalls to define ports with diameters between 25 and 125 μm .

Howitz et al disclose a device (Figure) comprising: fluid interface ports (capillaries containing menisci 6) formed in the side wall of a fluid channel (9) to provide access to the interior of the fluid channel, wherein a separation medium disposed in the interior of the fluid channel forms a virtual wall at each fluid interface port (Menisci 6). (Column 3, lines 11-15) Relevant to claim 6, they also disclose a fluid interface port comprising an array of apertures forming virtual walls.

Relevant to claim 39, Howitz et al disclose a method of sample injection comprising: forming a droplet from the liquid sample (Figure, droplet 5; Column 3, lines 31-34), and directing the droplet to a virtual wall formed by a liquid in a fluid interface port formed in the side wall of a flow channel.

Relevant to claims 40-45, they also disclose a method of forming their fluid interface ports, comprising the step of forming fluid interface ports in the channel sidewalls with diameter between 25 and 125 μm . (Column 3, lines 12-15, length and width are 50 μm)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Simpson et al by replacing the sample and waste reservoirs, and their associated side channels with a simple hole or holes through the sidewall to serve as a fluid port, as taught by Howitz et al, because Howitz et al teach the usefulness of their fluid port in introducing fluids to microchannels while preventing outflow of the fluid contained within the channel. (Column 1, lines 53-58) It would also reduce the number of holes required in the device by eliminating the need

for injection crosses, this reduction in the number of holes having been taught by Simpson et al to be desirable. (Column 3, lines 50-65)

Further addressing claims 1 and 5, given the definition of dead volume presented in the instant specification (roughly, the volume of liquid held in the port and not flowing with the fluid within the channel), the dead volume associated with ports such as those of Howitz et al will be variable, as a function of the affinities of the fluids for the surface of the port, among other factors. (Column 3, lines 25-31) As such, the dead volume will be zero or near zero (i.e. less than 1 picoliter) for a clean hydrophobic port surface in a device using aqueous fluids. Such hydrophobicity is an innate property of many polymers known to be useful in manufacturing microfluidic devices (e.g. fluoropolymers) or it could be achieved by using known surface treatments for glass (hexamethyldisilazane, used by Simpson - Column 4, lines 53-56) and silicon (Hydrofluoric acid), and would constitute an obvious modification of the device, because such a surface would minimize loss of the injected sample. (i.e. if an aqueous sample hit a hydrophobic surface in a port configured in the way shown in the Figure of Howitz et al, substantially the entire droplet would immediately fall into contact with the fluid in channel 9, as the contact angle and reduced frictional force would not be sufficient to retain the droplet on this surface)

Regarding the limitation that the port be wider than it is deep, although the example given by Howitz et al does not meet this limitation, Howitz et al also disclose variation of the depth of the port. (i.e. length of the capillary; Column 2, lines 5-10 and 27-30) Choice of a shorter length such that this limitation is met would have been

obvious to a skilled artisan, particularly given the trend towards miniaturization in this art.

Further addressing claim 20, by replacing each sample reservoir with a fluid interface port, and eliminating waste reservoirs, the number of holes in this combination device would be reduced to $N+A+C$, where N is the number of samples to be analyzed, A is the number of anode reservoirs, and C is the number of cathode reservoirs.

Regarding claim 39, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Simpson et al by altering the injection step by: forming a droplet of the sample and directing it to the virtual wall formed at a fluid interface port by a liquid in the separation channel (in the combination device of Simpson et al and Howitz et al described above), as taught by Howitz et al, because it would reduce waste of the sample liquid.

Regarding claims 40-45, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Simpson et al by replacing the step of forming sample reservoirs and associated side channels with the formation of a simple hole or holes (50 μm length and width) through the sidewall to serve as a fluid port, as taught by Howitz et al, because Howitz et al teach the usefulness of their fluid port in introducing fluids to microchannels while preventing outflow of the fluid contained within the channel. It would also reduce the number of holes required in the device by eliminating the need for injection crosses, this reduction in the number of holes having been taught by Simpson et al to be desirable. (Column 3, lines 50-65)

Regarding claims 46-48, each of these claims fully encompasses claim 1 in that they only recite limitations that are present in claim 1, while removing various other limitations. The prior art as applied to claim 1 above therefore also renders these claims obvious, given their open language (i.e. "comprising").

12. Claims 9-11 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al and Howitz et al as applied to claims 1 and 12 above, and further in view of Bjornson et al.

Simpson et al and Howitz et al disclose combinations as described above in addressing claims 1 and 12.

Neither Simpson et al nor Howitz et al disclose their devices being used for electrochromatography (Claims 9 and 27), pressure-driven chromatography (Claims 10 and 28), or isoelectric focusing (Claims 11 and 29).

Bjornson et al disclose electrophoretic devices used for isoelectric focusing and capillary chromatography. (Column 12, lines 53-59) They also disclose fluid flow in their devices by electroosmosis (Column 11, lines 55-60), which suggests electrochromatography. (i.e. chromatography in which the motion of the mobile phase is caused by an electric field)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of Simpson et al and Howitz et al by providing the separation capillaries with a chromatographic medium, immobilized pH gradient, or ampholytes and using the device for electrochromatography or isoelectric

focusing, as taught by Bjornson et al, because it would provide useful analytical data about the analytes. It would be well within the abilities of one having ordinary skill in the art to use the channel structure shown by Simpson et al with any known prior art capillary electrophoretic technique, such as those claimed here.

Additionally, electroosmotic force corresponds to a type of pressure driving a fluid through a capillary, and as such, is considered a form of pressure-driven chromatography.

13. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al and Howitz et al as applied to claim 36 above, and further in view of Sundberg et al.

Simpson et al and Howitz et al disclose a combination as described above in addressing claim 36. Simpson et al and Arnold et al also disclose a combination as described above in addressing claim 36.

None among Simpson et al, Howitz et al, and Arnold et al disclose a parallel loading device comprising a pin for carrying and introducing the droplet of a liquid sample to the fluid interface port by contacting the virtual wall.

Sundberg et al disclose a parallel loading device (Figure 2) comprising a pin (38) for carrying and introducing the droplet of a liquid sample (36) to the ports (34) of a microfluidic system.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of either Simpson et al and Howitz et al

or Simpson et al and Arnold et al by providing a parallel loading device comprising pins for carrying liquid samples to the fluid interface port, as taught by Sundberg et al, because it would simplify delivery of small droplets. It would be well within the abilities of one having ordinary skill in the art to choose any known means of delivering fluid droplets to a selected spot in a microfluidic device (i.e. the port), such as that taught by Sundberg et al. A technique that delivers a plurality of droplets simultaneously, such as that of Sundberg et al, would be particularly obvious to choose, because it would aid in increasing throughput, decreasing labor, etc.

14. Claims 1-3, 5-8, 12-24, 26, and 30-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al in view of Heller et al. (WO 99/64850) and either McCormick et al or Amigo. Since WO 99/64850 is in German, citations below are given to US Patent No. 6,846,398, which issued from the National Stage entry of this International Application.

The disclosure of Simpson et al is as described above in paragraph 9.

Heller et al disclose a device (Figures 1 and 2) comprising: fluid interface ports (A) formed in the side wall of a fluid channel to provide access to the interior of the fluid channel, wherein a separation medium is disposed in the interior of the fluid channel. (Column 5, lines 66-67) Relevant to claim 6, they also disclose a fluid interface port comprising an array of apertures. (Figures 1 and 2)

Relevant to claim 37, Heller et al disclose sample introduction via droplets on pins that guide the droplets to the interface port. (Column 6, lines 20-22)

Relevant to claim 39, Heller et al disclose a method of sample injection comprising: forming a droplet from the liquid sample, and directing the droplet to an interface formed by a liquid in a fluid interface port formed in the side wall of a flow channel. (Column 6, lines 18-33)

Relevant to claims 40-45, they also disclose a method of forming their fluid interface ports, comprising the step of forming fluid interface ports in the channel sidewalls with diameter matched to the channel width, which can be 10-hundreds of microns. (Figures 1 and 2; Column 5, line 66 - Column 6, line 2; the formation of the cover inherently involves this step)

Heller et al do not explicitly disclose the thickness of the cover used in preparing their interface ports.

McCormick et al disclose a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 13, lines 17-22)

Amigo discloses a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 8, lines 1-6)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Simpson et al by replacing the sample and waste reservoirs, and their associated side channels with a simple hole or holes through

Art Unit: 1753

the sidewall to serve as a fluid port, as taught by Heller et al, because Heller et al teach the that their fluid interface port increases the channel density attainable on microfluidic chips, and reduces sample consumption. (Column 2, lines 19-64) The benefits in efficiency and throughput would have been obvious and highly desirable to a skilled artisan. It would also reduce the number of holes required in the device by eliminating the need for sample and waste reservoirs, this reduction in the number of holes having been taught by Simpson et al to be desirable. (Column 3, lines 50-65)

It would also have been obvious to one having ordinary skill in the art to specifically use a thin cover plate, such as those taught by either McCormick et al or Amigo, because the silence of Heller et al concerning cover thickness suitable for forming the interface port indicates that a skilled artisan could choose any suitable cover thickness such as those known in the prior art, e.g. McCormick et al or Amigo. The choice of thinner material could be motivated by reduction of material consumption, which could potentially reduce manufacturing costs. For a conventional channel that has a width of tens to hundreds of microns, this would meet the limitation to a port that is wider than it is deep.

Regarding the limitations to a "virtual wall" and port dead volume of less than a picoliter or zero, whether the separation medium forms a meniscus at the interior or exterior surface of the port depends on the cross-sectional area of the port vs. that of the channel - fluid will naturally be drawn into the narrower opening, driven by its surface tension. Conventional HF glass etching is used by Simpson et al, which results in a channel that is approximately twice as wide as it is deep. (Column 4, lines 47-67)

An approximately hemicylindrical 60 micron wide, 30 micron deep channel would have a cross section of 450π square microns, while the port configuration of Figure 2 of Heller et al for this channel would be a circle with 60 micron diameter, having a cross section twice as large. In the absence of applied pressure, fluid in the channel would not be drawn into the port to a significant extent, and the meniscus would form at the bottom surface of the wall, leading to a port dead volume of substantially zero. Given a conventional flowable separation medium, this meniscus could only correspond to the instantly claimed "virtual wall", as no distinction between the respective ports, associated channels, or fluids can be seen. In addition, relatively deep channels with larger cross section than that of the port taught by Heller et al could also obviously be used, and in such cases fluid would be drawn into the port, forming a meniscus according to the limitations of claim 50.

Further addressing claim 20, by replacing each sample reservoir with a fluid interface port, and eliminating waste reservoirs, the number of holes in this combination device would be reduced to $N+A+C$, where N is the number of samples to be analyzed, A is the number of anode reservoirs, and C is the number of cathode reservoirs.

Regarding claim 37, it would have been obvious to one having ordinary skill in the art at the time the invention was made to introduce sample droplets to the interface port via pins that are guided to the ports, as taught by Heller et al, because it would provide a convenient means of transfer at a lower cost than a pipetting device.

Regarding claim 39, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Simpson et al by altering the injection step by: forming a droplet of the sample and directing it to the virtual wall formed at a fluid interface port by a liquid in the separation channel (in the combination device of Simpson et al and Heller et al described above), as taught by Heller et al, because it would reduce waste of the sample liquid.

Regarding claims 40-45, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Simpson et al by replacing the step of forming sample reservoirs and associated side channels with the formation of a simple hole or holes through the sidewall to serve as a fluid port, as taught by Heller et al, because Heller et al teach that their fluid interface port increases the channel density attainable on microfluidic chips, and reduces sample consumption. (Column 2, lines 19-64) The benefits in efficiency and throughput would have been obvious and highly desirable to a skilled artisan.

Regarding claims 46-48, each of these claims fully encompasses claim 1 in that they only recite limitations that are present in claim 1, while removing various other limitations. The prior art as applied to claim 1 above therefore also renders these claims obvious, given their open language (i.e. "comprising").

Regarding the independent claims, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as "coplanar" with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

15. Claims 9-11 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al, Heller et al, and either McCormick et al or Amigo as applied to claims 1 and 12 above, and further in view of Bjornson et al.

The reasoning for this rejection parallels that given above in paragraph 10.

Response to Arguments

16. Applicant's arguments filed 14 April 2006 have been fully considered but they are not persuasive.

Applicant's arguments are based on an unjustifiably narrow reading of the term "co-planar", which has no support in the specification. Applicant asserts that the limitation, "a meniscus that is substantially co-planar with the side wall of the channel in which the virtual wall is formed", as recited in the claims ". . . requires that the meniscus substantially align with the side wall at the top and bottom and have substantially the same thickness as the side wall, . . ." (Remarks, Page 12, 2nd full paragraph; Applicant's emphasis) There is no disclosure of such a meniscus in the specification as originally filed, and no reason to read the term "co-planar" so narrowly. Webster's Third International Dictionary defines "coplanar" as "lying or acting in the same plane". Accordingly, the Examiner considers a meniscus with any portion lying in the same plane as an interface port in a channel sidewall as reading on the claim as currently recited. It is the position of the Examiner that such a meniscus will exist in any device having the interface ports of Heller et al or Howitz et al, upon filling the channels of the

system with flowable media. A portion of the meniscus will inherently be in the plane of the port as described in the rejections above.

Applicant contends that Column 5, lines 30-37 of Heller et al teach away from a port that can form a virtual wall, as it teaches a port having a surface enlarged relative to the channel. This does not in any way teach away from a port that meets the limitations of the claim, as it merely teaches tapering of the port to aid in sample application in a certain embodiment. The meniscus properties described in the rejection above would not be altered by a tapering port.

Applicant claims that no adequate and objective reason for combining the references was given. The Examiner maintains that thinner covers could be used in the system of Heller et al, as in the McCormick and Amigo references, with the goal of reducing the amount of material used. It is reasonable to expect that the reduced material consumption would result in lower costs with scaled manufacture. Precision in thickness described by the Applicant is not required in the combination.

Applicant argues that the film described by Heller et al at Column 6, lines 1-2 somehow precludes the formation of a port in a sidewall. A solid film would certainly allow formation of sidewalls precisely as claimed, and as disclosed by Heller et al.

Applicant has provided no structural limitation that would distinguish the structure described by the prior art from that instantly claimed. The physical structure of the microfluidic system (i.e. channels, ports, plates) claimed by Applicant is the same as that described by the prior art. The behavior of a conventional fluid in forming a meniscus in these systems and the flow pattern of a fluid in channels having sidewall

ports as described in these systems would likewise be the same, and provides no basis for patentability.

Conclusion

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Jeffrey T. Barton whose telephone number is (571) 272-1307. The examiner can normally be reached on M-F 9:00AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam Nguyen can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JTB
5 July 2006



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